rate. *Radiat.Res.* 160: 543-548
3) Ogata H, Furukawa C, Kawakami Y and Magae J (2005). Quantitative Model for Evaluation of Dose Rates Effects on Biological Responses to Low Dose Gamma Radiation. *Radioprotection (in press)*
4) Sutton AJ et al. (2000). *Methods for Meta-Analysis in Medical Research*, Wiley, New York.
5) Stangl DK (2000). *Meta-Analysis in Medicine and Health Policy*, Marcel Dekker, New York.
6) Schmid CH (1999). Exploring heterogeneity in randomized trials via meta-analysis. *Drug Information J.* 33: 211-224

Fig.1 Relationship between ln(RR) and Doses by using meta-regression

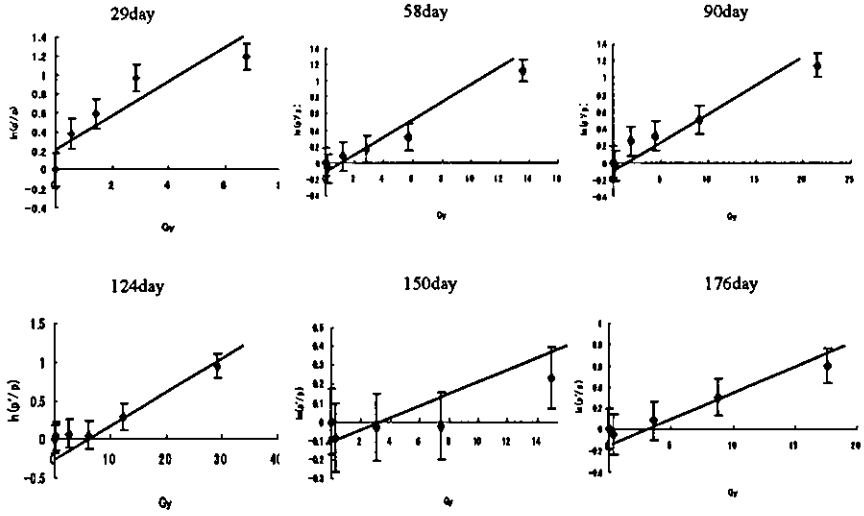


Fig.2 Meta-analysis on data of low dose/low dose rate

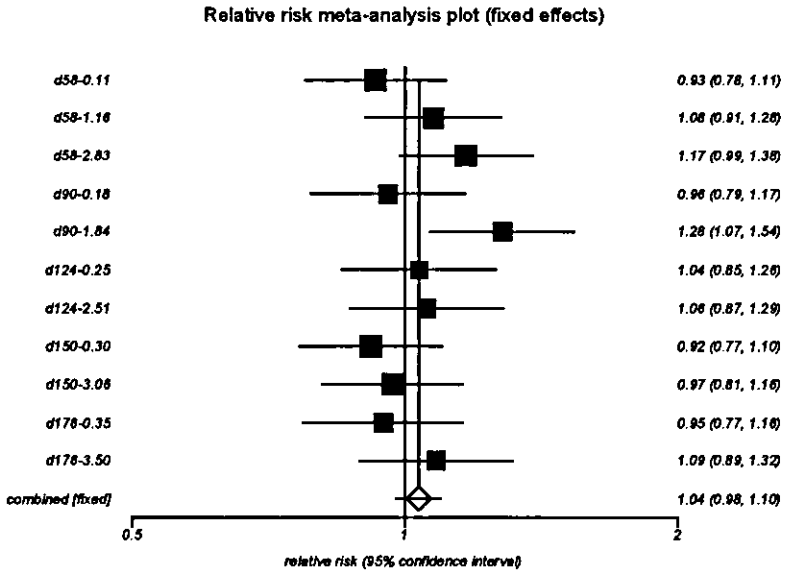
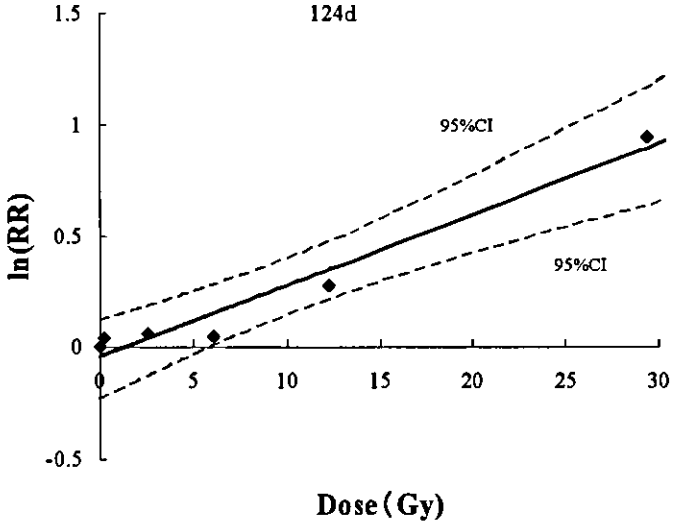


Fig.3 Confidence interval of meta-regression line



付録

国際シンポジウム「システマティックレビューとメタ・アナリシス」

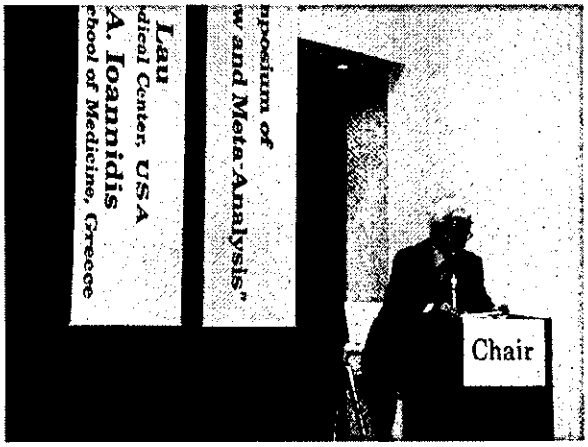
本研究班では、本年度の研究成果の発表会をかねるとともに、欧米のシステマティック・レビューとメタ・アナリシスの分野の第一人者の協力を得て、日本におけるメタ・アナリシスの普及のための国際シンポジウムを開催するため、（財）日本救急医療財団、医療技術評価総合研究推進事業研究成果等普及啓発事業へ下記の内容で研究成果発表の申請を行って実施された。

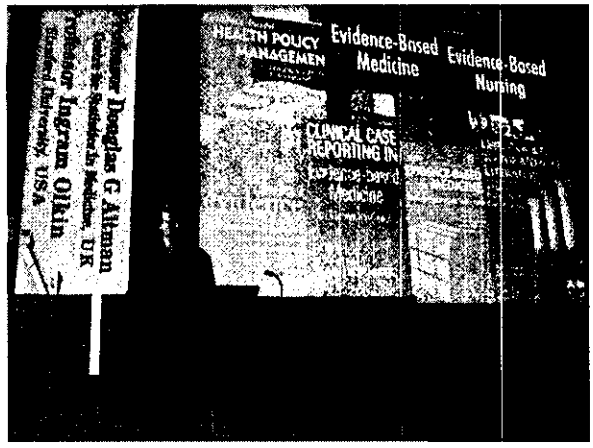
成果発表会申請内容の概要

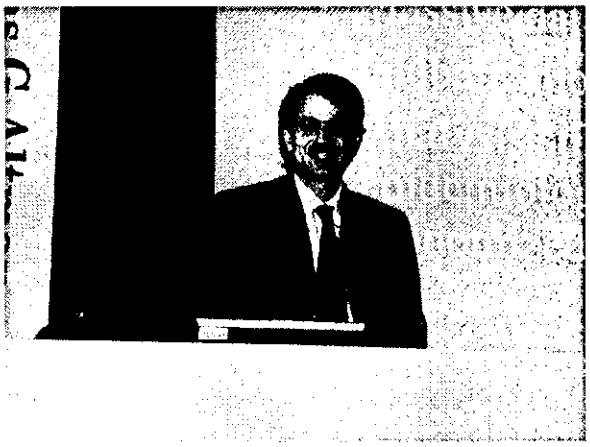
１．主任研究者氏名　　丹後 俊郎
　（所属機関）　　国立保健医療科学院
２．主任研究者の研究課題
　エビデンスを適切に統合するメタ・アナリシスの理論、応用と普及に関する調査研究
３．研究成果発表会のテーマ
　国際シンポジウム「システマティック・レビューとメタ・アナリシス」
４．研究成果発表会の開催日時
　日時：平成１７年２月２５日、８時３０分～１７時３０分
　場所：国立保健医療科学院 講堂

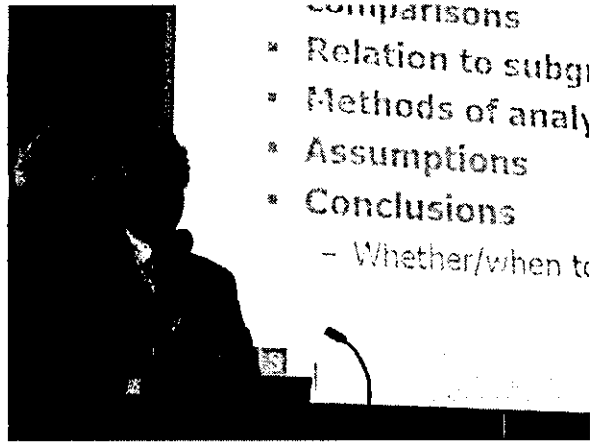
シンポジウムの参加者数は当日の降雪の交通機関の乱れにもかかわらず140名であった。発表者は招待講演４題、一般発表（ポスター）17題であった。発表者の氏名、所属、発表内容についてはアブストラクト集、招待講演者のパワーポイント資料等を添付するので参照のこと。

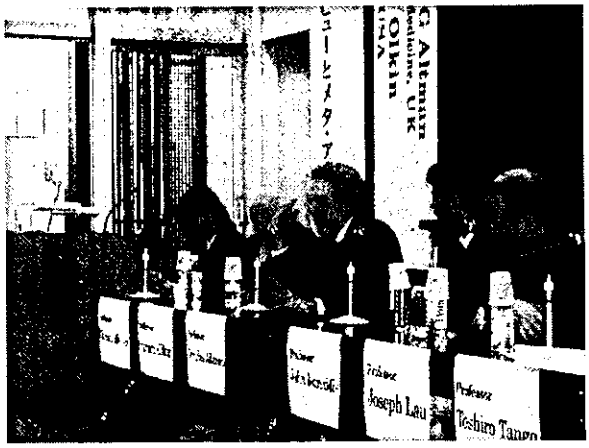
国際シンポジウムの風景










Joseph Lau

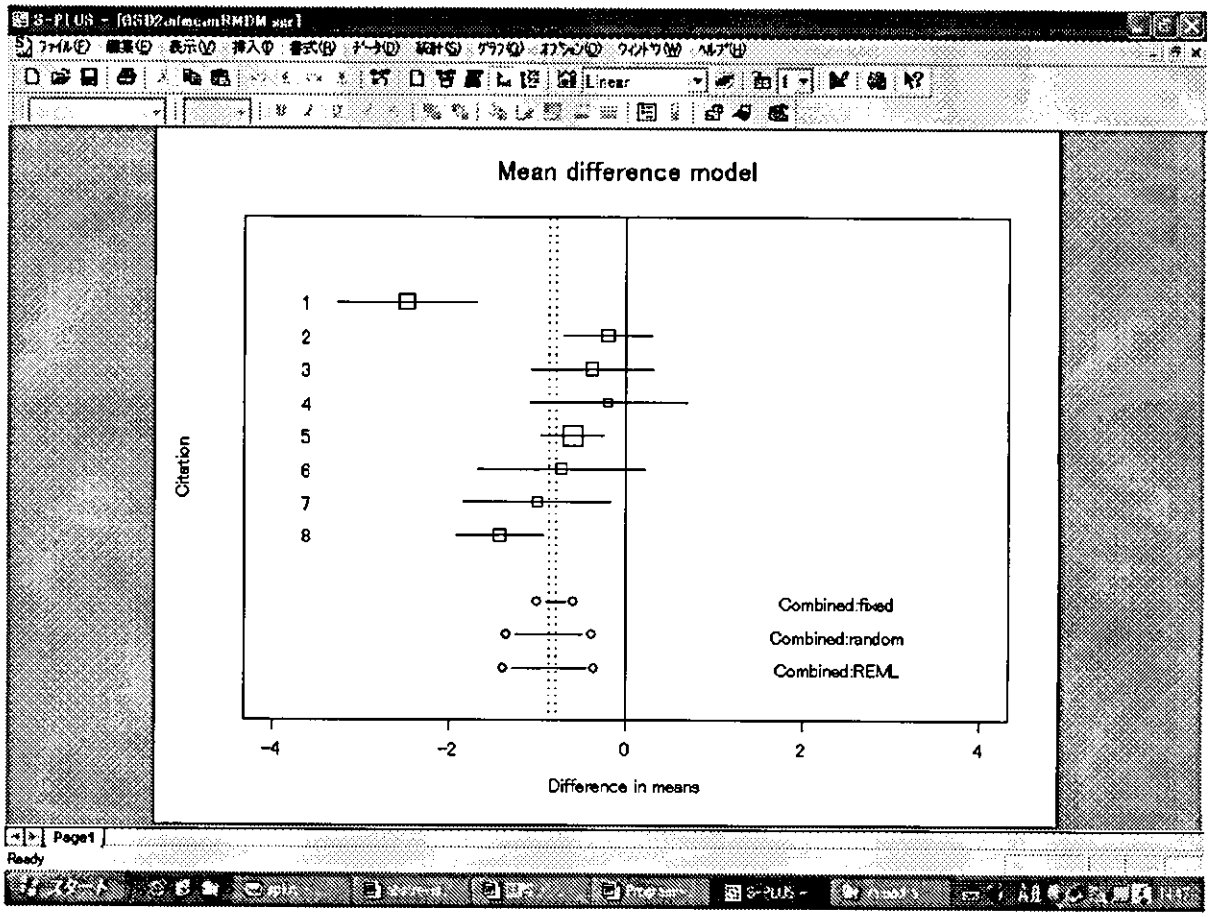

Professor
Professor


P-16

International Symposium of

"Systematic Review and Meta-Analysis"

Abstracts



25 February 2005
National Institute of Public Health (NIPH)
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February 2005

Dear Participants in this Symposium,

Welcome to Wako and the 2005 International Symposium: Systematic Review and Meta-Analysis ! I very much hope you will find the experience of the single-day-symposium enjoyable, as well as rewarding intellectually and professionally.

The symposium is designed to address current issues on meta-analysis by inviting the world foremost experts on systematic review and meta-analysis for technology assessment of health care. The meeting will also provide Japanese researchers with an opportunity for an exchange of ideas that will help accelerate current research, development and diffusion of meta-analysis and EBM.

I would like to thank four world leaders, Joseph Lau, John Ioannidis, Doug Altman and Ingram Olkin for their kind acceptance as invited speakers. Thanks also go to organizing committees together with symposium secretariat Yoko Nezu for their hard work and dedication in putting this international symposium together.

With best wishes for a most stimulating symposium

Toshiro Tango
Chair, Organizing Committee
Department of Technology Assessment and Biostatistics
National Institute of Public Health, Japan

International Symposium: Systematic Review and Meta-Analysis
Organizing Committee

Toshiro Tango (Chair)	National Institute of Public Health, Japan
Joseph Lau	Tufts-New England Medical Center, USA
Yoshinori Noguchi	Fujita Health University, Japan
Hideki Origasa	Toyama Medical and Pharmaceutical University, Japan
Kiichiro Tsutani	Graduate School of Pharmaceutical Sciences, the University of Tokyo, Japan
Kazue Yamaoka	National Institute of Public Health, Japan

Partnership:

Japan Council for Quality Health Care (JCQHC)
Japan Foundation for Emergency Medicine (JAFEM)
Japan Statistical Society (JSS)
Japanese Society for Pharmacoepidemiology (JSPE)
The Behaviormetric Society of Japan (BSJ)
The Biometric Society of Japan (JBS)
The Japanese Society of Clinical Pharmacology and Therapeutics (JSCPT)
The Japanese Society of General Medicine (JSGM)

Program

8:30 am Registration opens

Time for displaying poster (8:30 am - 9:15 am)

9:15 am - 9:25 am Opening address *Tango T, NIPH.*
9:25 am - 9:30 am Welcome address *Shinozaki H, President of NIPH.*

Session I : Invited Session (I)
Chair. Tsutani K, Graduate School of Pharmaceutical Sciences, the University of Tokyo, Japan.

9:30 am - 10:35 am Uses and impact of systematic reviews and meta analyses on clinical practice and healthcare.
Lau J, Tufts-New England Medical Center, USA.

10:35 am - 11:40 am Meta-analysis in molecular medicine.
Ioannidis J, University of Ioannina School of Medicine, Greece.

11:40 am - 11:50 am Compliments *Shimmura K, Ministry of Health, Labor and Welfare, Japan*

Lunch and looking at poster displays (11:40 am - 1:00 pm)

Session II : Invited Session (II)
Chair. Origasa H, Toyama Medical and Pharmaceutical University, Japan.

1:00 pm - 2:05 pm The issue of indirect comparisons in meta-analysis.
Altman D, Centre for Statistics in Medicine, Oxford, UK.

2:05 pm - 3:10 pm Graphical displays that might be helpful in interpreting medical data.
Olkin I, Stanford University, USA.

Session III : Panel discussion and floor discussion
Chair. Tango T, NIPH.
3:15 pm - 4:00 pm
Panelists. Lau J, Ioannidis J, Altman D, and Olkin I.
Interpreter. Misago C, Tsuda College, Japan.

Coffee Break (4:00 pm - 4:20 pm)

Session IV : Poster Sessions (Free discussions)
4:20 pm - 5:40 pm

6:00 pm - 8:00 pm Get-together party (at Restaurant, NIPH)

Invited Papers

I-01 Uses and impact of systematic reviews and meta-analyses on clinical practice and healthcare
Professor Joseph Lau
(Tufts-New England Medical Center, USA)

I-02 Meta-analysis in molecular medicine
Professor John P.A. Ioannidis
(University of Ioannina School of Medicine, Greece)

I-03 The issue of indirect comparisons in meta-analysis
Professor Douglas G Altman
(Centre for Statistics in Medicine, Oxford, UK)

I-04 Graphical displays that might be helpful in interpreting medical data
Professor Ingram Olkin
(Stanford University, USA)

Contributed Papers (Posters)

P-01 Bibilometric study of meta-analysis literatures, 1990-2003 *Nozoe A*

P-02 Comparison of cilostazol and ticlopidine coadministered with aspirin for long-term efficacy and safety after coronary stenting: A meta-analysis *Hashiguchi M, Ohno K, Kishino S, Mochizuki M, Shiga T*

P-03 Effects of dietary education to prevent type 2 diabetes mellitus: A meta-analysis *Yamaoka K, Tango T*

P-04 DNA repair gene XRCC1 polymorphism and lung cancer risk among Chinese people: A meta-analysis *Huang D, Guan P, He Q, Zhou B*

P-05 The effect of history of tuberculosis on the risk of lung cancer *Zhou B, Jiang D, He Q*

P-06 Effect of smoking on hearing loss: Quality assessment and meta-analysis *Nomura K, Nakao M, Morimoto T*

P-07 Blood levels of vitamin C and the subsequent risk of stroke in cohort studies: A systematic review *Yokoyama T, Tango T*

P-08 Comparison of effects in randomized, controlled trials with observational studies in digestive surgery *Shikata S, Nakayama T, Yamagishi H, Taji Y, Noguchi Y*

P-09 The quality of reporting of randomized controlled trials conducted in Japan: An evaluation based on the consort statement *Uetani K, Kimura Y, Ikai H, Yonemoto N, Nakayama T*

P-10 A meta-analytic comparison of echocardiographic stressors *Noguchi Y, Nagata-Kobayashi S, Stahl JE, Wong JB*

P-11 Does neuromuscular electrical stimulation strengthen the quadriceps femoris? A systematic review of randomized controlled trials *Bax L, Staes F, Verhagen AP*

P-12 The 'MIX' program, an active way of learning about meta-analysis with Excel *Bax L, Tsuruta H, Shirataka M, Takeuchi A, Ikeda N*

P-13 Concerns encountered in the meta-analysis of the causal relationship between coffee consumption and type 2 diabetes *Origasa H, Sakai H*

P-14 Confidence intervals for the ratio of regression slopes in meta-analysis *Takahashi K, Tango T*

P-15 Meta-analysis of low does radiation risk: An application of meta-regression model to biological risk evaluation *Ogata H*

P-16 Method of correcting for publication bias in meta-analysis *Matsuoka N, Hamada C*

P-17 Development of Clinical Trials Registry in Japan *Tsutani K, Kiuchi T, Ohashi Y, Uchida E, Matsuba H*

I-01

Uses and impact of systematic reviews and meta-analyses on clinical practice and healthcare

Joseph Lau, MD

Tufts-New England Medical Center, USA

The term "Evidence-Based Medicine (EBM)" was coined about a decade ago and it rapidly became a global phenomenon. EBM has attracted the interest of a diverse spectrum of people including researchers, clinicians, educators, students, patients, and healthcare policy decision makers. Systematic reviews and meta-analyses are the foundation on which EBM is based. These methodologies were developed in response to the growing needs of clinicians and researchers faced with the problem of the biomedical literature explosion. Many lacked the time to keep up with the ever-growing body of literature and the skills and resources necessary to synthesize and interpret this information.

A Google search performed on January 23, 2005 using the term "evidence-based medicine" found 1,190,000 items, 925,000 items for "systematic review," and 1,680,000 items for "meta-analysis." Even if only a fraction of these items are related to medicine or healthcare, the number of items found on the Internet rivals the number of primary research articles that systematic review and meta-analysis are supposed to address. EBM is not limited to medicine; it is gaining acceptance in other related healthcare fields such as dentistry, nursing, nutrition science, veterinary medicine, and health policy. People from many countries now participate in various types of EBM activities. The Cochrane Library is the best-known example of successes in systematic review and meta-analysis and an exemplary model of international collaboration.

Thousands of systematic reviews and meta-analyses have been published on healthcare interventions, evaluations of diagnostic tests, assessments of risks and prognosis. Many of these articles are published in high-ranking medical journals and many of these reviews have generated headline news and are affecting daily clinical decisions and healthcare policies. In the process, these publications have also influenced medical research agenda. Many professional organizations use systematic reviews in the development of clinical practice guidelines.

Systematic reviews are increasingly being used by government organizations as the evidentiary basis to inform healthcare policies and guide future research agenda. In the United

States, as an example, the FDA commissions systematic reviews to evaluate food health claims, the Center for Medicare and Medicaid Services (CMS) uses evidence reports and technology assessments to guide healthcare reimbursement decisions. The NIH Consensus Development Conferences now regularly relies on comprehensive evidence reports as part of the conference process. Many other countries use systematic reviews and meta-analyses similarly.

The impact of systematic reviews and meta-analyses is just beginning to be felt. It is relatively easy to demonstrate that a specific intervention saves or improves lives but it is difficult to do so for a systematic review or a meta-analysis. However, several striking examples such as pre-natal use of corticosteroids to reduce mortality in premature births and intravenous thrombolytic therapy for acute myocardial infarction offer glimpses of the potential values of meta-analyses conducted in a timely manner.

Successes notwithstanding, there are critics of meta-analysis. Some of their criticisms have been addressed in the past decade with the development of new methods and empirical research in systematic review and meta-analysis. These efforts have led to a better foundation for understanding of heterogeneity, metrics, and interpretation of meta-analysis results. Recommendations from this body of research hopefully will also lead to better conduct and report of primary research. The advent of human genomics presents new challenges in summarizing and interpreting a large and diverse body of information. In the future, systematic reviews and meta-analyses must also be produced in real time to increase their usefulness and impact.

Meta-analysis in molecular medicine

John P.A. Ioannidis, MD

Professor and Chairman, Department of Hygiene and Epidemiology, University of Ioannina School of Medicine, Ioannina, Greece; Professor of Medicine (adjunct), Tufts University School of Medicine, Boston, USA

Meta-analysis is currently finding a widening circle of applications in molecular medicine. The rapid advent of technology in the basic sciences has generated very interesting challenges for the integration of biomedical information. Meta-analysis can help to make sense of the rapidly accumulated data and may be a useful link in the translation of this basic information to meaningful results and clinical use. Meta-analysis can also be a prime tool for dissecting biases and other sources of heterogeneity in these data. Several of the biases in this literature are similar to what is already known from the more traditional literature of clinical research. There are however also additional problems that stem from peculiarities of specific molecular science fields. The talk will try to cover some of the most promising applications of meta-analysis in molecular medicine, including genetics and genomics, predictive biomarkers, and microarrays. Special emphasis will be given to issues of heterogeneity and bias, including differences in early vs. subsequent research, rapid alternation of extreme results (Proteus phenomenon), small vs. large studies, standardization issues, outcome reporting biases, language bias, impact of measurement error (e.g. deviation from Hardy-Weinberg equilibrium in genetic association studies), empirical evidence on ancestry effects and other subgroup differences, validation challenges, and issues in the clinical interpretation of the results. We will also discuss the advantages and disadvantages of evolving concepts such as meta-analysis of individual participant data, study registration, data collection/investigator registration, and the creation of multicenter international networks in this field. Finally, a scheme for grading the evidence in molecular research will be proposed.

The issue of indirect comparisons in meta-analysis

Douglas G Altman

Centre for Statistics in Medicine, Oxford, UK

Background:

The randomised controlled trial (RCT) is the most valid design for evaluating the relative efficacy of health care interventions. However, many competing interventions have not been directly compared in RCTs. For example, each of two drugs may have been compared to placebo in RCTs but they have not been compared directly. A comparison based on comparing two sets of trials is known as an 'indirect' comparison.

Indirect methods are common in meta-analyses, but they are subject to greater bias (especially selection bias) than 'head-to-head' randomised comparisons, as the benefit of randomisation does not hold across trials. An equivalent problem arises when we wish to compare two subsets of trials within a meta-analysis, for example based on trial characteristics, study quality, or the precise interventions (e.g. dose). It is important to understand the additional issues that arise in such analyses as they may lead to inaccuracies in the estimates of treatment effects and result in inappropriate policy decisions.

This talk will discuss the findings of a large project[1,2] with the following objectives:

- To survey the frequency of use of indirect comparisons in systematic reviews and evaluate the methods used in their analysis and interpretation
- To identify alternative statistical approaches for the analysis of indirect comparisons and assess their properties
- To carry out empirical work comparing direct and indirect estimates of the same effects within reviews.

Methods:

(a) The Database of Abstracts of Reviews of Effectiveness (DARE) was searched for systematic reviews involving meta-analysis of RCTs which reported both direct and indirect comparisons, or indirect comparisons alone.

(b) A systematic review of Medline and other databases was made to identify published methods for analysing indirect comparisons.

(c) A resampling study was carried out using data from the large International Stroke Trial. Results of indirect comparisons were compared with direct comparisons and also theoretical results.

Results:

Of systematic reviews that included meta-analyses of two or more RCTs, 31/327 (9.5%) included indirect comparisons. Few studies had carried out a formal analysis. Some reviews based analysis on the naïve addition of data from the treatment arms of interest. Interpretation of indirect comparisons was not always appropriate.

In most cases, results of adjusted indirect comparisons mostly agreed reasonably well with those of direct comparisons. A significant discrepancy ($P < 0.05$) was observed in just three of the 44 comparisons between the direct and the adjusted indirect estimates. The direction of discrepancy between the two estimates was inconsistent.

Rather few relevant methodological papers were identified. The resampling study showed that the naïve method is liable to severe bias and also produces over-precise answers. Several other methods will be described that provide correct answers, although they rely on strong but unverifiable assumptions inherent in the indirect framework. Four times as many similar sized trials are needed for the indirect approach to have the same power as directly randomised comparisons.

Conclusions:

When conducting systematic reviews to evaluate the effectiveness of interventions, direct evidence from good quality RCTs should be used wherever possible. When there is no or insufficient direct evidence from RCTs, the adjusted indirect comparison may provide useful or supplementary information on the relative efficacy of competing interventions.

Several valid methods of analysis exist for making adjusted indirect comparisons, but interpretations should be more cautious in view of the observational nature of the data. The validity of the adjusted indirect comparisons depends on the internal validity and similarity of the included trials. Adjusted indirect comparisons usually but not always agree with the results of head-to-head randomised trials. If both direct and indirect comparisons are possible within a systematic review, these should be done separately before considering whether to pool data.

Song F, Altman DG, Glenny A-M, Deeks JJ. Validity of indirect comparison for estimating efficacy of competing interventions: empirical evidence from published meta-analyses. *BMJ* 2003;326:472–474.

Glenny A-M, Altman DG, Song F, Sakarovitch C, Deeks JJ, D'Amico R, Bradburn M, Eastwood A. Indirect comparisons of competing interventions. *Health Technology Assessment*, in press

Graphical displays that might be helpful in interpreting medical data

Ingram Olkin

Stanford University, USA

The primary output in almost all medical meta-analyses is a diagram that displays the confidence intervals for treatment-control comparisons for each study, together with a combined confidence interval for the overall effect. When there are important subgroups, as for example, sex differences or age categories, there will also be a combined effect within the subgroups. In general the measures of treatment-control effects are based on standardized mean differences for continuous data and risk differences, odds ratios, or risk ratios for proportion data.

These studies also provide considerable data on the demographics of the samples. Some studies will use a regression model to take account of these demographic variables. However, the relationship among the demographic variables and their relation to the outcome measures has not been well-understood. Because of the advances in computational power, visual maps can be created that display these relationships. These maps often help in the interpretation of the data. In this talk we show one particular method that is based on multidimensional scaling methodology, and apply it to explore the relationships among the studies of quality improvement for diabetes. The primary purpose of multidimensional scaling is to develop a map that represents the proximities between observations or events. Medical applications of this methodology has primarily been in cancer genetics: assaying the relationship between multiple proteins, genes, or patient characteristics and tumor characteristics.

Diagnostic data provides another area in which visualization can be useful, especially in the use of resampling methods to provide confidence bands for ROC curves. A particular example deals with the accuracy of calcaneal quantitative ultrasound as a diagnostic criterion for osteoporosis.